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# Formulation Design of Double-layer in the Outer Shell of Dry-coated Tablet to Modulate Lag Time and Time-controlled Dissolution Function: Studies on Micronized Ethylcellulose for Dosage Form Design (VII)

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## ABSTRACT

The dry-coated tablet with optimal lag time was designed to simulate the dosing time of drug administration according to the physiological needs. Different compositions of ethylcellulose (EC) powder with a coarse particle (167.5 μm) and several fine particles (<6 μm), respectively, were mixed to formulate the whole layer of the outer shell of dry-coated tablets. The formulations containing different weight ratios of coarse/fine particles of EC powders or 167.5 μm EC powder/excipient in the upper layer of the outer shell to influence the release behavior of sodium diclofenac from dry-coated tablet were also explored. The results indicate that sodium diclofenac released from all the dry-coated tablets exhibited an initial lag period, followed by a stage of rapid drug release. When the mixture of the coarse/fine particles of EC powders was incorporated into the whole layer, the lag time was almost the same. The outer shell broke into 2 halves to make a rapid drug release after the lag time, which belonged to the time-controlled disruption of release mechanism. When the lower layer in the outer shell was composed of 167.5 μm EC powder and the upper layer was formulated by mixing different weight ratios of 167.5 μm and 6 μm of EC powders, the drug release also exhibited a time-controlled disruption behavior. Its lag time might be freely modulated, depending on the amount of 6 μm EC powder added. Once different excipients were respectively incorporated into the upper layer of the outer shell, different release mechanisms were observed as follows: time-controlled explosion for Explotab, disruption for Avicel and spray-dried lactose, erosion for dibasic calcium phosphate anhydrate, and sigmoidal profile for hydroxypropyl methylcellulose.

**KEYWORDS:** micronized ethylcellulose, dry-coated tablet, outer layer, time-controlled dissolution, lag time.

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## INTRODUCTION

From the viewpoint of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable[1]. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system.[2] Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs.[3] Optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. Although many controlled-release preparations have been developed, the drug preparation according to the concept of chronotherapy should be preferably to deliver the drug in a pulsatile fashion, rather than a continuous delivery.[4-5] This drug delivery aims to improve the therapeutic efficacy by varying drug release in accordance with patient need (ie, the ideal drug delivery system should involve a non-delivery period rather than a continuous delivery period). For solid dosage forms, chronotherapy is achieved by the use of slowed-release coatings to delay the release of one or more drugs until an approximate predetermined time period.[6-7]

A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration.[8-9] This novel system is not only rate controlled but is also time controlled. The dry-coated tablet prepared by a unique compression press consists of an inner core and an outer shell. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture. To design a novel dry-coated tablet, the outer shell is a critical layer in ensuring reliable tolerance to reach the predetermined site. Our previous studies have found that different particle sizes of ethylcellulose (EC) powders might be used to act as an outer shell to directly prepare the dry-coated tablet with different lag time and time-controlled dissolution functions.[10-12] The lag time and time-controlled dissolution were effectively controlled by the amounts and types of materials (excipients, EC) incorporated into the inner core and/or outer shell, and different compression forces of both layers of the dry-coated tablet. For chronotherapeutic delivery, the formulation is designed

**Table 1.** Physical Properties of Different Grades of Ethylcellulose Powders

| Grades | N7F | N10F | N22F | N7G |
|---|---|---|---|---|
| Lot No. | 011032 | 012037 | 102043 | 402147 |
| Average particle size (μm)* | 4.0 | 4.6 | 6.0 | 167.5 |
| Viscosity (cps)† | 6.2 | 9.6 | 22.0 | 6.2 |
| MW‡ | 58000 | 80000 | 123000 | 58000 |

*Particle size was determined by laser-particle size analyzer.

†Viscosity was measured at 25°C of a 5% (wt/wt) solution in a solvent mixture of toluene and ethanol (80:20) by weight.

‡MW indicates weight-average molecular weight.

to control the lag time occurring prior to the substantial release of drug.[4-5]

It is well known that the micromeritic characterization of powders plays an important role for the preparation of solid dosage forms, particularly in the automatic manufacturing process. In order to perform the semi- or complete automatic manufacturing process for the preparation of dry-coated tablets, EC powders with 167.5 μm size may be selected as a major component in the outer shell owing to its better flowability and compressibility (Table 1).[13-14] However, our previous studies showed that the lag time for the dry-coated tablet prepared by this size of EC powder was only 4 hours, too short to delay the release as is necessary.[10] On the other hand, the dry-coated tablets prepared by fine particle sizes (<6.0 μm) possessed a longer lag time.

In order to achieve the development of a dry-coated tablet with optimal lag time, different compositions of EC powder with particle size of 167.5 μm and each of the fine particle sizes (<6 μm) of EC powders as listed in Table 1 were mixed to formulate the whole layer of outer shell in this study. The effect of formulations containing different weight ratios of coarse and fine particle sizes of EC powders in the upper layer of the outer shell of dry-coated tablets on the release behavior of sodium diclofenac from dry-coated tablets was investigated. Moreover, the influence of formulations containing different excipients in the upper layer of the outer shell on the lag time and release mechanism of sodium diclofenac from dry-coated tablets was also explored.

## Materials and Methods

### *Materials*

Sodium diclofenac (<80 mesh, water content <5%, Syn-Tech Chem and Pharm Co, Ltd, Taiwan, ROC) was used. Four grades of EC with different particle sizes (N7F: 4.0 μm, N10F: 4.6 μm, N22F: 6.0 μm, N7G: 167.5 μm) were gifts from Shin-Etsu Chem Ind Co, Ltd (Tokyo, Japan), as listed in Table 1.[13-14] Five pharmaceutical excipients, sodium starch glycolate (Explotab, Edward Mendell Co, Inc, Penwest, Danbury, CT), microcrystalline cellulose (Avicel PH 101, <50 μm, Asahi Kasei Co, Ltd, Tokyo, Japan), spray-dried lactose (<100 μm, Dairy Crest Ltd, Surrey, UK), dibasic calcium phosphate anhydrate (DCPA, Kyowa Chem Ind Co, Tokyo, Japan), and hydroxypropyl methylcellulose (HPMC, Metolose 60SH-4000, <50 μm, Shin-Etsu Chem Ind Co, Ltd, Tokyo, Japan), were used. The other materials were reagent grade purchased from the market.

### *Preparation and Evaluation of Dry-coated Tablets*

#### *Standard Preparation Method*

The standard dry-coated tablet was prepared by using an infrared (IR) spectrophotometric hydraulic press (Riken Seiki Co, Tokyo, Japan) under constant pressure, as described in our previous studies.[10-12] An inner core tablet (sodium diclofenac, 100 mg; 7 mm in diameter) was directly compacted under the pressure of 200 kg/cm$^2$ for 1 minute. One-hundred-forty milligrams of EC powder was first filled into a die having a diameter of 10 mm, and then the inner core tablet was manually placed in the center of the EC powder. The remaining 140 mg of EC powder was then poured into the die and compressed at 300 kg/cm$^2$ for 1 minute to prepare the dry-coated tablet (total weight: 380 mg). Here, EC powder was used as an outer shell; however, it might be replaced by the following EC mixture or EC/excipient mixture.

#### *Different Formulations for the Outer Shell of Dry-coated Tablet*

The formulation of the outer shell for the dry-coated tablet was respectively prepared using the following formulas:

(1) Whole layer of the outer shell
   (a) EC powder (N7F, N10F, N22F, or N7G)
   (b) EC mixture (weight ratio = 1:1): N7G:N7F, N7G:N10F, or N7G:N22F

(2) Double layer of the outer shell
   (a) EC mixture: *lower layer*: N7G; *upper layer*: N7G:N22F (weight ratio = 3:1, 6:1, or 9:1)
   (b) EC/excipient mixture: *lower layer*: N7G; *upper layer*: N7G: excipient (weight ratio = 6:1)

All tablets were ~4.18 ± 0.23 mm in thickness and 9.98 ± 0.07 mm in diameter, determined using a digital caliper (Mitsutoyo, Tokyo, Japan).

*Dissolution Study*

Drug release from each dry-coated tablet was determined in 900 mL of distilled water (pH 5.6) using a *United States Pharmacopeia (USP)* dissolution paddle assembly (NRT-VS3, Toyama SanGyo Co, Ltd, Tokyo, Japan) at 100 rpm and 37 ± 0.5°C. The concentration of sodium diclofenac released from dry-coated tablets was determined spectrophotometrically at 276 nm (UV-160 A, Shimadzu Co, Kyoto, Japan). All dissolution studies were performed in triplicate to obtain the mean and SD.

## Results and Discussion

### *Drug Release From Dry-coated Tablets Prepared by Whole Layer with EC Powder or EC Mixture in the Outer Shell*

Figure 1 shows the release behavior of sodium diclofenac from these dry-coated tablets when the whole layer of outer shell for dry-coated tablets was formulated with EC powder or EC mixture. Obviously, the drug release from all dry-coated tablets exhibited an initial lag period, followed by a stage of rapid drug release. After that lag time, the outer shell of the dry-coated tablets broke into 2 halves to make a rapid drug release in distilled water. The lag time was 4.0, 12.3, 16.3, or 20.3 hours for dry-coated tablets prepared by only using N7G (167.5 μm), N22F (6.0 μm), N10F (4.6 μm), or N7F (4.0 μm) powders, respectively. The finer the EC particle size used the longer the lag time obtained, suggesting the particle size of EC powder could modulate the timing of drug release from such dry-coated tablets. This clearly indicates that the particle size of EC powder significantly influenced the compactness of dry-coated tablets to prevent solvent penetration, leading to delaying the drug release. In order to increase the lag time of dry-coated tablets prepared by N7G powder alone, the fine particle size of EC powder such as N22F, N10F, or N7F was respectively mixed with N7G powder by 1:1 weight ratio. It is evident that the lag time was increased from 4 hours to 18 hours after mixing with fine particle size EC powders. This lag time was almost the same (~18 hours); there was no significant difference among these dry-coated tablets. This finding might be because the fine EC powder was filled into the interparticulate and/or intraparticulate porosity of coarse EC powder by Van der Waals to form a more compact EC layer in the outer shell, leading to prolonged disruption time.[15] This release mechanism belonged to time-controlled disruption, as shown in Figure 2A. However, it is interesting to note that both a faster disruption and a quicker dissolution behavior were found for the dry-coated tablet prepared by the EC mixture than was found for the dry-coated tablet prepared by one of the EC powders having a faster disruption but delaying dissolution process, since a sharp slope of dissolution profile was obtained for the dry-coated tablet prepared by EC mixture.

### *Drug Release From Dry-coated Tablets Prepared by EC*

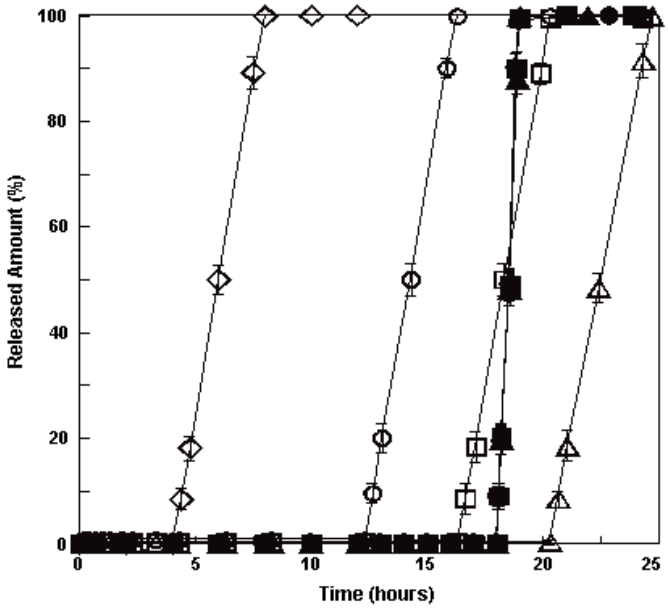


**Figure 1.** Dissolution profiles of sodium diclofenac from dry-coated tablets in distilled water. Different particle sizes of EC: △, 4.0 mm (N7F); □, 4.6 mm (N10F); ○, 6.0 mm (N22F); and ◇, 167.5 mm (N7G). Different EC mixtures (weight ratio = 1:1):▲, N7G:N7F; ■, N7G:N10F; ●, N7G:N22F (mean ± SD, n = 3).

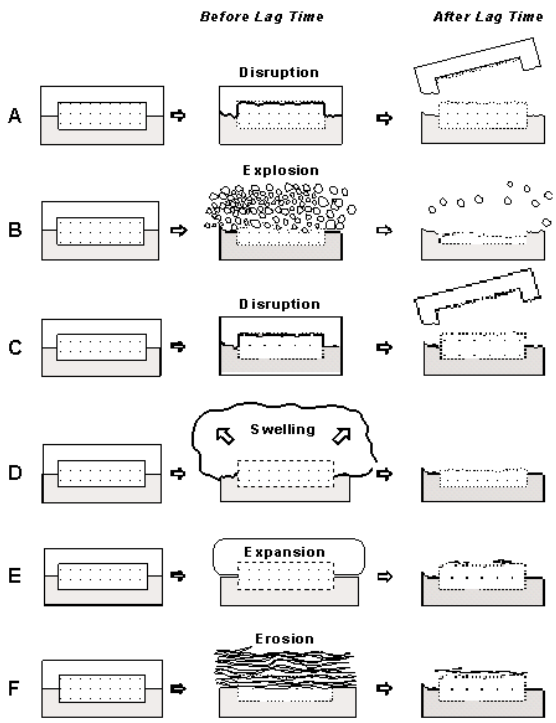


**Figure 2.** Schematic dissolution process for drug released from dry-coated tablets prepared by different formulations: (A) N7G:N22F (weight ratio = 1:1 or 6:1); (B) N7G:Explotab (weight ratio = 6:1); (C) N7G:Avicel (weight ratio = 6:1); (D) N7G:HPMC (weight ratio = 6:1); (E) N7G:spray-dried lactose (weight ratio = 6:1); (F) N7G:DCPA (weight ratio = 6:1).

### *Mixture in the Upper Layer of Outer Shell*

In order to modulate the lag time of drug release ranging from 4 hours to 18 hours, the double layer in the outer shell of dry-coated tablets was designed. The lower layer of outer shell was still made of N7G (167.5 μm), but the upper layer was formulated by mixing different weight ratios (3:1, 6:1, or 9:1) of N7G and N22F (6.0 μm). Apparently, the drug release from this type of dry-coated tablet also exhibited an initial lag period, followed by a faster stage of drug release (Figure 3). It clearly reveals that the dissolution behavior of sodium diclofenac released from this type of dry-coated tablet still belonged to the time-controlled disruption function (Figure 2A). The lag time was 8, 6, or 4 hours for dry-coated tablets prepared by weight ratio of N7G and N22F with 3:1, 6:1, or 9:1, respectively. Beyond the lag time, the outer shell of dry-coated tablets also broke into 2 halves to make a rapid drug release. By increasing the amount of N7G powder in the upper layer of the outer shell, the lag time of drug release from dry-coated tablets became shorter. The amount of fine particle size of N22F added might play an important role in monitoring the lag period of tablet disruption. However, the dissolution profile of the dry-coated tablet prepared by EC mixture in the upper layer with weight ratios of N7G:N22F (9:1) was somewhat different from the others beyond the lag time of a stage of drug release. The small amount of fine N22F powder added in the mixture of N7G:N22F (9:1) might slightly consolidate the compact of mixture in the upper layer, leading to delaying the drug release behavior, although its lag time was almost the same as the lag time of the upper layer prepared by N7G alone. The relationship between the lag time of drug dissolution and the amount of N7G used is shown in Figure 4. Obviously, the amount of N7G within 70% to 90% might significantly change the lag time of drug release from dry-coated tablets. Moreover, the loose packing of EC mixture occurring in the middle area of the lateral surface of dry-coated tablets seems to be responsible for this tablet disruption (Figure 2A). This loose packing at the lateral surface allowed water channels for solvent penetration to cause the lateral cleavage of dry-coated tablet, leading to rapid drug release.[16] After rapid disruption, 2 halves of outer coating shells were observed in the dissolution medium.

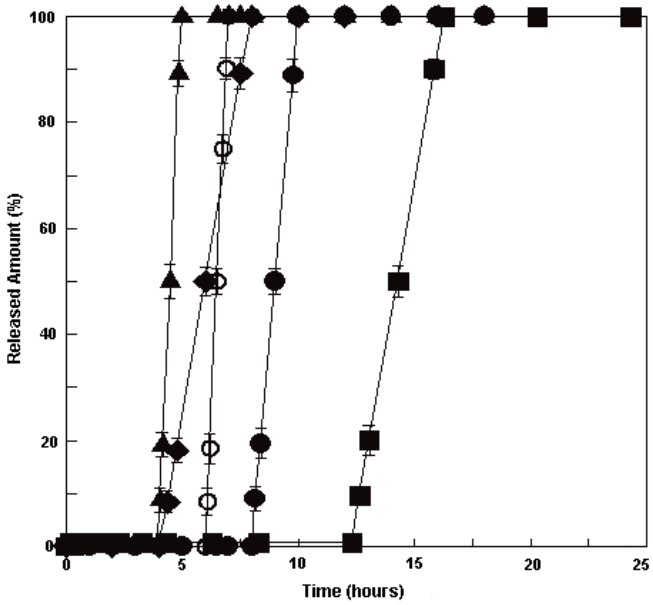


**Figure 3.** Drug release from dry-coated tablets prepared by EC mixture in the upper layer of the outer shell. Dry-coated tablets prepared by lower layer with N7G and upper layer with different weight ratios of N7G:N22F (▲, 1:0; ◆, 9:1; ○, 6:1; ●, 3:1; ■, 0:1) (mean ± SD, n = 3).

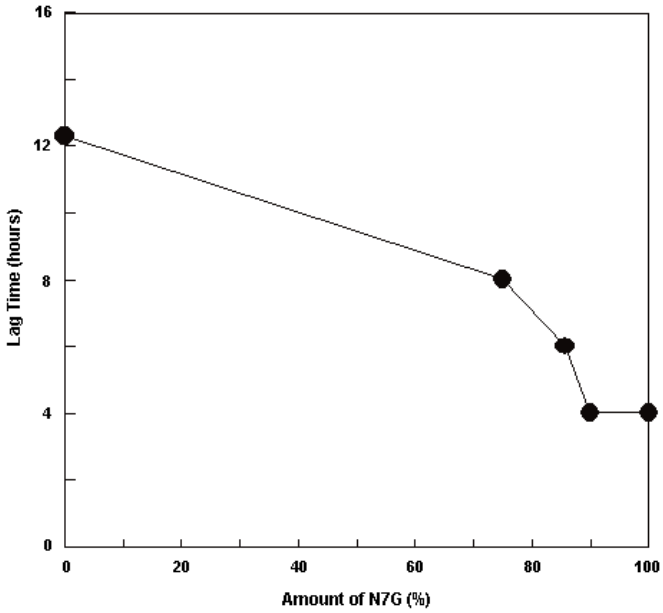


**Figure 4.** Relationship between the lag time of drug released from dry-coated tablet and the amount of N7G used.

### *Drug Release From Dry-coated Tablets Prepared by EC Powder/Excipient Mixture in the Upper Layer of Outer Shell*

Figure 5 illustrates the effect of the incorporation of different EC/excipient mixtures in the upper layer of the outer shell for dry-coated tablets. The lower layer was composed of N7G powder alone, but the upper layer was formulated by N7G/excipient mixture with a constant weight ratio of 6:1. Different dissolution behaviors were observed from each different dry-coated tablet, as shown in Figure 2. There was scanty drug-excipient interaction to affect the dissolution mechanism of drug since the excipient coexisted with EC powder in the upper layer of dry-coated tablets. The excipient might predisintegrate in the dissolution medium. When Explotab was mixed with N7G and loaded on the upper layer of the outer shell, the lag period was markedly shortened to ~40 minutes, and drug release was faster after lag time. This result might be due to the quick disintegration of the upper

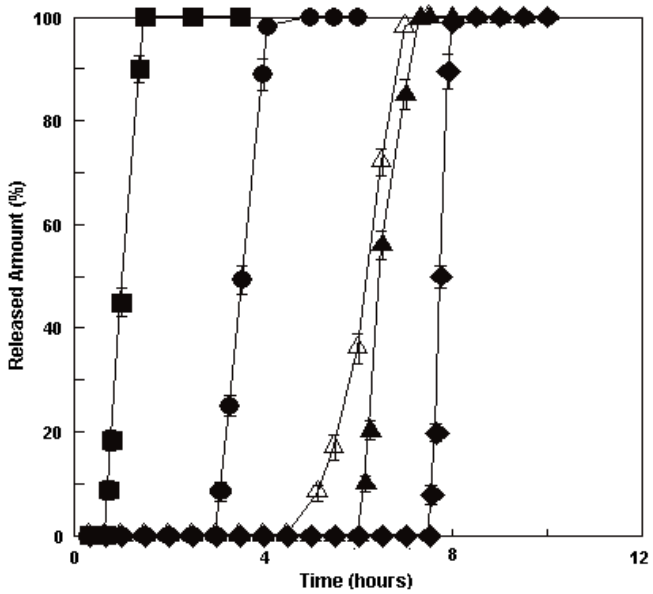


**Figure 5.** Drug release from dry-coated tablets prepared by the mixture of EC powder/excipient in the upper layer of the outer shell. The weight ratio of N7G and excipient (6:1); Type of excipient: ■, Explotab; ●, Avicel; △, HPMC; ▲, spray-dried lactose; ◆, DCPA (mean ± SD, n = 3).

layer, leading to faster dissolution. Explotab as a superdisintegrant might be responsible for the rapid uptake of water and swelling, resulting in the quick explosion or disintegration (Figure 2B).[17] It should be noted that although Explotab belongs to an anionic disintegrant, it may cause some slight in vitro binding with cationic drugs but it is not a problem in vivo. Many commercial sodium diclofenac products still used Explotab as a disintegrant in the pharmaceutical market.

If Avicel was incorporated into the formulation of the upper layer, the dissolution behavior of this dry-coated tablet was similar to that prepared by EC powder. After 3 hours of lag time, the dry-coated tablet was also broken into 2 halves through the lateral surface to result in a subsequent rapid release of sodium diclofenac (Figure 2C). Although Avicel is a minor disintegrant, a small amount of Avicel did not improve the disintegration of tablet.[18-19] However, the hydrophilic property of Avicel seems to improve the solvent penetration from the lateral surface of dry-coated tablets, leading to a shorter lag time than for tablets prepared by EC powder.

Once hydroxypropyl methylcellulose (HPMC) was added into the upper layer of dry-coated tablets, the lag time of dry-coated tablets was ~5.5 hours, but a sigmoidal dissolution profile was obtained. The initial viscous layer of HPMC and the formation of expansive and swelling layer above the lower layer might delay the disintegration of the inner core tablet.[20] However, the hydrophilic property of HPMC might also improve the dissolution of drug, resulting in a sigmoidal profile at the initial stage, as shown in Figure 2D. With the increase of stirring time, the gel was dispersed or dissolved into dissolution medium. Sodium diclofenac was quickly released from the inner core, leading to a faster release profile (Figure 5). It should be noted that the lag time for this dry-coated tablet with a double layer was ~5.5 hours, but the lag time for a dry-coated tablet prepared by whole layer of mixture of HPMC and EC powder was 12.4 hours.[12] Moreover, the drug release mechanism of dry-coated tablets prepared by double layer or whole layer in the outer shell seems to be different. This finding suggests that the dosage form designed by the double layer might monitor the disintegration and dissolution behavior of preparations.

When spray-dried lactose was formulated into the upper layer of dry-coated tablets, the lag time of dry-coated tablets was ~6.0 hours and a slight swelling behavior was also observed (Figure 2E). The soluble spray-dried lactose might facilitate the faster disintegration of the swelling layer, resulting in a shorter lag time. This result may also compare with our previous study in which the lag time was 8.5 hours for the whole layer of dry-coated tablets prepared by the mixture of spray-dried lactose and EC powder.[12] Once dibasic calcium phosphate anhydrate (DCPA) was contained in the upper layer of a dry-coated tablet, the lag time was ~7.5 hours and the time-controlled erosion behavior from the dry-coated tablet was apparently observed (Figure 2F). This slightly longer lag time might be attributed to the DCPA, which not only acted as a directly compressible excipient but also provided a retarding effect on the release of sodium diclofenac from the dry-coated tablet, as compared with the above excipients used or a whole layer with N7G powder alone.[21-22]

## Conclusion

The lag time and time-controlled release behavior of sodium diclofenac from dry-coated tablets could be monitored by changing the particle sizes of EC powders in the whole layer of the outer shell, different weight ratio of large/fine particle mixture, or types of excipient used in the upper layer of the outer shell. In particular, different drug release mechanisms were observed by incorporating different excipients into the upper layer in the outer shell of the dry-coated tablet.

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